METHODS OF THE TREATMENT OF PSORIATIC ARTHRITIS USING (+)-2-[1-(3-ETHOXY-4-METHOXYPHENYL)-2-METHYLSULFONYLETHYL]-4-ACETYLAMINOISOINDOLINE-1,3-DIONE

This application is a continuation-in-part of U.S. patent application Ser. No. 11/106,142, filed Apr. 13, 2005, which is a divisional of Ser. No. 10/392,195, filed Mar. 19, 2003, now U.S. Pat. No. 6,962,940, which claims the benefit of U.S. Provisional Application No. 60/366,515, filed Mar. 20, 2002 and U.S. Provisional Application No. 60/438,450, filed Jan. 7, 2003. Each of the above is incorporated herein by reference in their entireties.

1. FIELD OF THE INVENTION

This invention provides methods of treating, preventing and/or managing psoriatic arthritis by the administration of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione, substantially free of its (−) enantiomer, alone or in combination with other therapeutics. The invention also provides pharmaceutical compositions and dosage forms comprising specific amounts of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione suitable for use in methods of treating, preventing and/or managing psoriatic arthritis.

2. BACKGROUND OF THE INVENTION

2.1 Psoriatic Arthritis

Psoriatic arthritis is a chronic inflammatory arthritic condition affecting the skin, the joints, the insertion sites of tendons, ligaments, and fascia. Gladman, *Current Opinion in Rheumatology*, "Current concepts in psoriatic arthritis," 2002, 14:361–366, and Ruddy et al., *Rheumatology, vol.* 2., chapter 71, page 1071, 6^{th} ed., 2001. Psoriatic arthritis is commonly associated with psoriasis. Id. Approximately 7% of patients with psoriasis develop psoriatic arthritis. *The Merck Manual,* 448 (17^{th} ed., 1999).

Psoriatic arthritis may appear in a variety of clinical patterns. There are five general patterns of psoriatic arthritis: arthritis of the distal interphalangeal joints, destructive arthritis, symmetric polyarthritis indistinguishable from rheumatoid arthritis, asymmetric oligoarthritis, and spondyloarthropathy. Ruddy et al., page 1073. Psoriasis appears to precede the onset of psoriatic arthritis in 60–80% of patients. Occasionally, arthritis and psoriasis appear simultaneously. Cutaneous eruptions may be preceded by the arthropathy.

Symptoms of psoriatic arthritis include extra bone formation, joint stiffness, dactylitis, enthesopathy, tendonitis, and spondylitis. Gladman, page 362. Most patients have the classic psoriasis pattern of skin lesions. Ruddy et al., page 1075. Scaly, erythematous plaques; guttate lesions, lakes of pus, and erythroderma are psoriatic skin lesions that may be seen in patients with psoriatic arthritis. Nail lesions, including pitting, Beau lines, leukonychia, onycholysis, oil spots, subungual hyperkeratosis, splinter hemorrhages, spotted lunulae, and cracking, are clinical features significantly associated with the development of psoriatic arthritis. Ruddy et al., page 1076. Ocular symptoms in psoriatic arthritis include conjunctivitis, iritis, episcleritis, keratoconjunctivitis sicca and aortic insufficiency.

Although the exact cause of psoriatic arthritis is unknown, genetic, environmental, immunologic, and vascular factors contribute to one's predisposition. Ruddy et al., pages 1071–72, and Gladman, page 363. The disease is more likely to occur in first-degree relatives who are affected than in the general population. Ruddy et al., page 1071. Population studies have shown that multiple human leukocyte antigens (HLA) are associated. British Society for Rheumatology, *Rheumatology,* 2001; 40:243, and Gladman, page 362. Much evidence suggests that a T-cell-mediated process drives the pathophysiology of psoriatic arthritis. Ruddy et al., pages 1071 and 1077, and Gladman, page 363. Activated T cells may contribute to the enhanced production of cytokines found in synovial fluid. Thl cytokines (e,g., tumor necrosis factor-alpha (TNF-alpha), interleukin (IL)-1-beta and IL-10) are more prevalent in psoriatic arthritis than in rheumatoid arthritis, suggesting that the two diseases may result from a different mechanism. Ruddy et al., page 1071. Monocytes also play a role in psoriatic arthritis and are responsible for the production of matrix metalloproteinases, which may mediate the destructive changes in the joints of patients with psoriatic arthritis. Gladman, page 364.

Internationally, the incidence of psoriatic arthritis is 1–40%. Psoriatic arthritis usually develops in the fourth to sixth decades of life, but it can occur at almost any age. Men and women are affected equally, but a male predominance occurs in the spondylitic form, while a female predominance occurs in the rheumatoid form. Ruddy et al., page 1077.

There is a significant need for safe and effective methods of treating, preventing and managing psoriatic arthritis, particularly for patients that are refractory to conventional treatments. In addition, there is a need to treat such disease while reducing or avoiding the toxicity and/or side effects associated with conventional therapies.

3. SUMMARY OF THE INVENTION

In one aspect, the invention provides methods of treating, preventing and/or managing psoriatic arthritis in humans in need thereof. The methods comprise administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonyl-ethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate (e.g., hydrate) or clathrate thereof, substantially free of its (−) enantiomer.

In some embodiments, the methods further comprise the administration of a therapeutically or prophylactically effective amount of at least a second active agent, including but not limited to, an anti-inflammatory agent, an immnunosuppressant, mycophenolate mofetil, a biologic agent, or a Cox-2 inhibitor.

In another embodiment, (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate (e.g., hydrate) or clathrate thereof is administered orally in a dosage form such as a tablet and a capsule.

In further embodiments, (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, or a pharmaceutically acceptable prodrug, metabolite, polymorph, salt, solvate (e.g., hydrate) or clathrate thereof is administered topically in a dosage form such as ointments, creams, gels, pastes, dusting powders, lotions, sprays, liniments, poultices, aerosols, solutions, emulsions and suspensions.

In another aspect, the invention provides pharmaceutical compositions for treating, preventing and/or managing psoriatic arthritis comprising (+)-2-[1-(3-ethoxy-4-methox-